CHAPTER 1
Diabetic ketoacidosis in adults

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Introduction

Diabetic ketoacidosis (DKA) is an acute complication of diabetes mellitus. It is characterized by the triad of hyperglycemia, ketosis, and metabolic acidosis.\(^1\) DKA complicates mainly patients with Type 1 diabetes mellitus, where it may be the first manifestation of the disease, and rarely people with Type 2 diabetes.\(^1\) A special heterogeneous syndrome of “ketosis-prone diabetes (KPD),” in usually adult patients who may lack the typical clinical phenotype of autoimmune Type 1 diabetes, has recently been identified. While initially the condition was thought to be limited to persons of non-Caucasian ethnicity (African-Americans and Hispanics), its prevalence appears to be increasing worldwide.\(^2\) DKA is an emergency situation and hospitalization of the patient is necessary for immediate treatment. Its frequency is reported as 4.8–8.0 episodes per 1000 diabetic patients.\(^3,4\) The mortality rate is 2.5–9% and increases along with age, level of consciousness on admission, degree of hyperosmolality and acidosis, as well as severity of azotemia.\(^5,6\) In the US, hospitalizations due to DKA reach 100,000 and the cost of treatment has been reported as 1 billion dollars per year.\(^7\)

Summary box

- DKA is characterized by the triad of hyperglycemia, ketosis, and acidosis
- DKA complicates mainly Type 1 diabetes

Definition and classification of DKA in adults

The criteria for the diagnosis of DKA are shown in Table 1.1.\textsuperscript{8,9} DKA can be mild, moderate, or severe. It is considered severe when the arterial blood pH is less than 7.0, the concentration of plasma bicarbonate is less than 10 mEq/L, and the anion gap is greater than

<table>
<thead>
<tr>
<th>Diagnostic criteria and classification</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>&gt;250 mg/dl</td>
<td>&gt;250 mg/dl</td>
</tr>
<tr>
<td>(&gt;13.9 mmol/L)</td>
<td>(&gt;13.9 mmol/L)</td>
<td>(&gt;13.9 mmol/L)</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15–18</td>
<td>10–14</td>
</tr>
<tr>
<td>Serum ketone*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Urine ketone*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective serum osmolality\textsuperscript{†}</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Anion gap (mEq/L)\textsuperscript{‡}</td>
<td>&gt;10</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Alert/drowsy</td>
</tr>
</tbody>
</table>

* Determination of serum or urine ketone is usually based on a nitroprusside-based reaction.

\textsuperscript{†} Calculation: effective serum osmolality: $2 \times \text{measured Na}^+ (\text{mEq/L}) + \text{glucose (mg/dl)/18} = \text{mOsm/kg}$ or effective plasma osmolality: $2 \times \text{measured Na}^+ (\text{mmol/L}) + \text{glucose (mmol/L)} = \text{mOsm/kg}$. Normal range = 285–295 mOsm/kg.

\textsuperscript{‡} Calculation: anion gap = (Na\textsuperscript{+}) – [(Cl\textsuperscript{−}) + (HCO\textsubscript{3}\textsuperscript{−})] mEq/L. Normal range = 12 (±3) mEq/L.

Modified from reference 8 with permission.
12 mEq/L. In severe DKA, the patient is in stupor or in coma. Notably, the severity of DKA does not necessarily coincide with the degree of hyperglycemia.

DKA can rarely be seen without marked hyperglycemia (euglycemic DKA), and in one series of 722 consecutive episodes of DKA only 1.1% had blood glucose levels less than 180 mg/dl (10 mmol/L). Relatively euglycemic DKA has been reported in patients using subcutaneous insulin infusion pumps, which contain short-acting insulin. In these patients, interruption of insulin delivery results in rapid development of ketosis, as patients become insulin deficient within 2–4 hours of cessation of insulin delivery. Euglycemic DKA has also been reported during pregnancy and in subjects using conventional insulin regimens. In these cases, the secretion of large amounts of glucose in the urine or lower rates of hepatic glucose production may account for the relatively “low” glucose concentrations. Moreover, prolonged fasting before the onset of DKA may result in a lower increase in blood glucose than non-fasting.

Since the mid 1990s, increasing attention has been focused on a heterogeneous condition characterized by presentation with DKA in patients who do not necessarily fit the typical characteristics of autoimmune Type 1 diabetes. Earlier reports used the terms “atypical diabetes,” “Flatbush diabetes,” “diabetes type 1B,” and “ketosis-prone type 2 diabetes mellitus” to describe subsets of this condition. It was noted that in some instances patients presented with DKA as the first manifestation of diabetes and subsequently evolved to insulin independence. This condition, now called “ketosis-prone diabetes (KPD),” comprises a group of atypical diabetes syndromes characterized by severe β-cell dysfunction (manifested by presentation with DKA or unprovoked ketosis) and a variable clinical course. To date, the best attempt to differentiate patients with KPD into clinically distinct subgroups has resulted in the so-called Aβ classification, based on the presence (A+) or absence (A−) of pancreatic autoantibodies (anti-GAD65 [glutamic acid decarboxylase] and/or anti-IA-2 [islet-antigen autoantibody-2]) and the presence or absence of β-cell functional reserve, as measured by a fasting or glucagon-stimulated C-peptide level. Thus, the four subgroups are defined as follows:

- A+β− autoantibodies present, β-cell function absent
- A+β+ autoantibodies present, β-cell function present
- A−β− autoantibodies absent, β-cell function absent
- A−β+ autoantibodies absent, β-cell function present.
A+β− and A−β− patients are immunologically and genetically distinct from each other but share clinical characteristics of Type 1 diabetes, with decreased β-cell function, and both subgroups would be termed Type 1 diabetes (Type 1A and 1B) in the current American Diabetes Association (ADA) classification system. A+β+ and A−β+ patients are immunologically and genetically distinct from each other but share clinical characteristics of Type 2 diabetes, with preserved β-cell functional reserve, and would be termed Type 2 diabetes in the ADA scheme. A−β+ patients comprise the largest KPD subgroup (approximately 50%)\(^\text{12}\) and are also the patients who most commonly come to the notice of physicians because they present with DKA yet have the clinical features and subsequent behavior of Type 2 diabetes.\(^\text{13}\) Most A−β+ subjects have new-onset diabetes and are obese, middle-aged males with a strong family history of Type 2 diabetes. In these patients, β-cell function is substantial when measured within 1–2 weeks of the index DKA and improves further when measured after 6–12 months.\(^\text{11}\)

### Summary box
- DKA is classified as mild, moderate, or severe
- In severe DKA, altered mental status is the rule
- The degree of DKA does not coincide with the degree of hyperglycemia
- DKA can rarely be seen without marked hyperglycemia
- Ketosis-prone diabetes is a new heterogeneous condition seen in adults presenting with ketoacidosis and having a variable subsequent course

### Predisposing factors for DKA

DKA can be the first manifestation of Type 1 diabetes in 10–30% of cases.\(^\text{4,5,14}\) With regard to the remaining cases, DKA is caused by factors associated with either increase in insulin needs (serious infections, trauma or surgery where insulin resistance suddenly and dramatically increases) or decrease of insulin availability (deliberate discontinuation of treatment, dysfunction of infusion systems, inappropriate changes of insulin doses, or mistakes in insulin delivery). In several series, infections were the commonest (28–43%) identifiable cause of DKA followed by errors in insulin delivery or non-
Box 1.1 Precipitating factors of diabetic ketoacidosis

- Infections (mainly lower respiratory tract and urinary tract infections)
- Inappropriate insulin dosage or deliberate omission of insulin therapy
  - non-compliance
  - psychiatric disorders
  - fear of weight gain
  - fear of hypoglycemia
- Cardiovascular disease
- Severe injury
- Hyperthyroidism
- Pregnancy
- Alcohol abuse
- Other co-morbidities (e.g., pancreatitis)
- Drugs
  - corticosteroids
  - pentamidine
  - sympatheticomimetic drugs
  - high dosage of diuretics
  - some antipsychotic drugs

compliance (18–26%). DKA may be precipitated in patients with Type 2 diabetes during the course of overwhelming infections and less commonly during acute myocardial infarction or trauma. The contributing factors to the development of DKA in patients with known diabetes are depicted in Box 1.1.9 Regarding KPD patients, approximately 50% of A–β+ KPD patients have new-onset diabetes and develop DKA without a clinically evident precipitating factor (“unprovoked” A–β+ KPD), while the remainder have long-standing diabetes prior to presentation with DKA, and develop ketoacidosis in association with an acute illness or non-compliance with antidiabetic treatment (“provoked” A–β+ KPD). Unprovoked A–β+ KPD patients display a striking male predominance (2.6:1 male:female) that is quite distinct from provoked A–β+ KPD patients (0.7:1).15 Unprovoked A–β+ KPD patients show a better prognosis regarding insulin independence compared to the provoked A–β+ KPD group.
Chapter 1

Pathogenesis

The combined effect of reduced insulin concentrations (absolute or relative, but always serious) and elevated concentrations of the counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) leads to hyperglycemia, ketosis, dehydration, and electrolyte disturbances.\(^6,10\) It is of note that, in the absence of insulin deficiency, elevated levels of the counter-regulatory hormones per se do not cause ketosis.\(^6\) The fundamental difference between DKA and hyperosmolar hyperglycemic state (HHS) is that small residual amounts of insulin in HHS can prevent significant ketosis and, therefore, acidosis. The pathogenesis of DKA and of HHS is depicted in Figure 1.1.

**Summary box**

- DKA is the first manifestation of Type 1 diabetes in 10–30% of cases
- Infections and errors in insulin delivery or non-compliance are the commonest precipitating factors for DKA

**Pathogenesis**

<table>
<thead>
<tr>
<th>Absolute insulin deficiency</th>
<th>Counter-regulatory hormones</th>
<th>Relative insulin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipolysis</td>
<td>Protein synthesis</td>
<td>Absent or minimal ketogenesis</td>
</tr>
<tr>
<td>FFA to liver</td>
<td>Proteolysis</td>
<td></td>
</tr>
<tr>
<td>Ketogenesis</td>
<td>Gluconeogenic substrates</td>
<td></td>
</tr>
<tr>
<td>Glucose utilization</td>
<td>Glycogenolysis</td>
<td></td>
</tr>
<tr>
<td>Alkali reserve</td>
<td>Ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Triacylglycerol</td>
<td>Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Glycosuria (osmotic diuresis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of water and electrolytes</td>
<td>Decreased fluid intake</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td></td>
<td>Hyperosmolarity</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.1** Pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Adapted (with modification) from reference 9 with permission.
Hyperglycemia

Hyperglycemia in DKA is the result of reduced glucose uptake and utilization from the liver, muscle, and fat tissue and increased gluconeogenesis as well as glycogenolysis. The lack of insulin results in an increase in gluconeogenesis, primarily in the liver but also in the kidney, and increased glycogenolysis in liver and muscle. In addition, the inhibitory effect of insulin on glucagon secretion is abolished and plasma glucagon levels increase. The increase of glucagon aggravates hyperglycemia by enhancing gluconeogenesis and glycogenolysis. In parallel, the increased concentrations of the other counter-regulatory hormones enhance further gluconeogenesis. In addition to increased gluconeogenesis, in DKA there is excess production of substances which are used as a substrate for endogenous glucose production. Thus, the amino acids glutamine and alanine increase because of enhanced proteolysis and reduced protein synthesis.

Hyperglycemia-induced osmotic diuresis leads to dehydration, hyperosmolality, electrolyte loss (Na⁺, K⁺, Mg²⁺, PO₄³⁻, Cl⁻, and Ca²⁺), and eventually decline in glomerular filtration rate. With decline in renal function, glucosuria diminishes and hyperglycemia worsens. Dehydration results in augmentation of plasma osmolality, which results in water movement out of the cells to the extracellular space. Osmotic diuresis caused by hyperglycemia results in loss of sodium in urine; in addition, the excess of glucagon aggravates hyponatremia because it inhibits reabsorption of sodium in the kidneys. With impaired insulin action and hyperosmolality, utilization of potassium by skeletal muscles is markedly decreased leading to intracellular potassium deficiency. Potassium is also lost due to osmotic diuresis. In addition, metabolic acidosis leads to extracellular movement of potassium in exchange for H⁺, which may be lost in vomit or urine. Moreover, potassium transport is reinforced by protein catabolism due to insulin depletion. Therefore, patients with DKA may present initially with low, normal, or even high serum potassium levels. Nevertheless, a normal serum potassium level in DKA indicates a large body potassium deficit and institution of insulin therapy will lead to future hypokalemia.

The grade of hyperglycemia in DKA varies but rarely exceeds 800 mg/dl (44.4 mmol/L). On the contrary, in HHS, hyperglycemia is usually greater and plasma glucose may exceed 1000 mg/dl (55 mmol/L).
Ketonemia and metabolic acidosis

In DKA, insulin deficiency and increased levels of catabolic hormones (particularly catecholamines) promote breakdown of adipose tissue triglycerides (lipolysis). Concurrently, re-esterification of free fatty acids (FFAs) to triglycerides in adipose tissue is impaired by insulin deficiency. This combination results in the release into the circulation of large quantities of FFAs, which via the portal vein reach the liver. There, in the absence of insulin, FFAs are not converted to triglycerides as normally happens, and they are used, after they have entered the mitochondria, for the production of ketones (or ketone bodies), a procedure facilitated by the elevated glucagon levels. Thus, liver is the site for ketone formation.

The first ketone body produced is acetoacetic acid, which then is reduced to either β-hydroxy-butryrate (β-OHB) or acetone. β-hydroxy-butryrate is the most abundant ketone (75%) to accumulate in blood in DKA. With the exception of acetone, ketone bodies are strong organic acids that dissociate fully at physiological pH, generating equimolar amounts of H⁺ and ketoanions. The rapid increase in plasma H⁺ concentration outstrips the buffering capacity of the body fluids and tissues and metabolic acidosis develops.

Elimination of ketone bodies (ketolysis) from the body occurs in the mitochondria of organs that can use ketone bodies as an alternative energy source. Skeletal muscle is the main tissue that contributes to ketolysis. Some ketone bodies are eliminated in urine. The anionic charge of ketones leads to excretion of positively charged ions like sodium, potassium, calcium, and magnesium in urine, compounding the loss of water and electrolytes caused by glucosuria. Acetone is excreted via the lungs and produces the characteristic smell of the breath (like nail-varnish remover) in patients with DKA.

Summary box

- DKA is due to the combined effect of reduced insulin concentrations and elevated levels of the counter-regulatory hormones
- Reduced glucose uptake and utilization and increased gluconeogenesis as well as increased glycogenolysis result in hyperglycemia
Clinical presentation

The cardinal manifestations of DKA are increasing polydipsia and polyuria, generalized weakness, and altered mental status. In the case of newly diagnosed Type 1 diabetes, variable but rapid weight loss occurs. Symptoms usually develop over several days to weeks. Deep and rapid respiration (Kussmaul respiration) is the result of metabolic acidosis. Signs of dehydration and hypovolemia such as hypotension, orthostatic hypotension, tachycardia, poor skin turgor, and dry mucous membranes are often found. Decreased skin turgor suggests 5% dehydration. An orthostatic change in pulse alone suggests a 10% loss of extravascular fluid volume, whereas an orthostatic change in pulse and blood pressure (increase of 15 beats/min and decrease of 10 mmHg) suggests a 15–20% fluid deficit. Supine hypotension indicates either severe dehydration (fluid loss >20%) or underlying sepsis.

Nausea, vomiting, and abdominal pain may be present in DKA. Generalized abdominal pain is more common in young patients with severe acidosis and can mimic a surgical emergency (pseudoperitonitis). Abdominal pain has been associated with acidosis and resolves with treatment. A succussion splash may be evident on examination due to gastric stasis.

Some impairment in mental status is common in DKA, although coma occurs in only 10% of patients. Cerebral edema must always be considered in patients whose consciousness level declines during treatment, although subclinical cerebral edema may be present in DKA before initiation of treatment.

Acidosis induces peripheral vasodilation, which in combination with hypotension may lead to hypothermia and mask infection. In
such cases the rectal temperature should be taken. Obtaining a
history and performing an examination to diagnose precipitating
causes are important.

Summary box

- Symptoms of DKA include polydipsia, polyuria, malaise, nausea,
vomiting, and abdominal pain
- Findings on clinical examination include Kussmaul respiration,
signs of dehydration, and altered mental status
- Abdominal pain in severe DKA may mimic a surgical emergency

Laboratory findings

The tests that should be included in the initial laboratory investiga-
tion when diabetic ketoacidosis is suspected are shown in Box 1.2.6
As shown in Table 1.1, arterial pH is low depending on the severity
of acidosis. In severe DKA pH values in the range of 6.7–6.8 have
been observed.

DKA is a high anion gap metabolic acidosis. The anion gap is
calculated using the formula:

$$(\text{Na}^+) - [(\text{Cl}^-) + (\text{HCO}_3^-)]$$

Box 1.2 Initial laboratory assessment of a patient with
suspected diabetic ketoacidosis

- Arterial blood gases
- Serum urea or blood urea nitrogen
- Serum creatinine
- Serum electrolytes (K$^+$, Na$^+$, Mg$^{2+}$, P$^{3+}$, Cl$^-$, Ca$^{2+}$)
- Complete blood count with differential
- Serum osmolality
- Urinalysis
- Serum or urine ketones
- Blood and urine cultures, when infection is suspected
- Pregnancy test in women of reproductive age
- Electrocardiogram
- HbA$_{1c}$
The normal value of the gap is 12 (±3) mEq/L. The anion gap should be corrected by the degree of hypoalbuminemia (add 2.5 mEq/L to the calculated anion gap for every 1.0 g/dl [10 g/L] decrease in serum albumin levels less than 4.5 g/dl [45 g/L]). The severity of acidosis depends on the rate of formation of ketone bodies, the duration for which they have been produced (patients who immediately attend medical treatment have more benign acidosis), and their excretion rate in urine (patients with near normal renal function have the ability to increase $H^+$ excretion, thereby reducing the severity of acidosis). An anion gap greater than 12 mEq/L suggests anion gap acidosis, while a plasma bicarbonate level greater than 18 mEq/L rules out metabolic acidosis. Arterial PO$_2$ concentration is increased and PCO$_2$ is diminished in patients with normal respiratory function as a result of compensatory hyperventilation.$^6,8,10$

Detection of ketone bodies in either serum or urine is usually performed via specific dipsticks that rely on the nitroprusside reaction, which colors the stick purple-violet. It should be noted that these sticks are essentially specific for acetoacetate; they do not react with $\beta$-OHB and react only weakly with acetone. During treatment of DKA, 3-OHB is converted to acetoacetate; therefore, nitroprusside-based tests may give the mistaken impression that DKA is either worsening or not resolving. In addition, the test can give false negative results in patients being treated with agents containing sulfhydryl groups (for example captopril) and false positive results if the dipsticks have been exposed to air for a long time.$^6,8,10$

In recent years most biochemical laboratories have measured serum $\beta$-OHB directly by spectrophotometry, thus ruling out false results obtained by blood or urine strips. Moreover, some newer glucose meters can measure $\beta$-OHB in capillary blood using an electrochemical method with specific strips. The normal level of $\beta$-OHB in serum or in capillary blood is <0.5 mmol/L; in DKA values >1.0 mmol/L are usually found. Determination of serum or capillary $\beta$-OHB levels has a higher sensitivity and specificity than determination of urine ketone bodies for the diagnosis of DKA.$^{16}$ As mentioned above, $\beta$-OHB is an early and abundant ketoacid indicative of ketosis. Acetoacetate (determined by the nitroprusside method) may be negative in the blood in early DKA.

DKA is characterized by a significant loss of water and electrolytes. This is a result of osmotic diuresis due to glycosuria as well
as ketonuria. Despite the contribution of ketonuria, the degree of dehydration in DKA is usually lower than in HHS because the latter arises more gradually and insidiously. Other factors also may contribute to dehydration, such as nausea, vomiting, use of diuretics, and fever.⁶,⁸,¹⁰

Osmotic diuresis results in electrolyte loss (K⁺, Na⁺, Mg²⁺, PO₄³⁻, Cl⁻, Ca²⁺). The average deficit of water and electrolytes in DKA is shown in Table 1.2. As mentioned above, serum potassium levels are usually normal, but they may be low or even elevated.

The initial serum sodium concentrations are usually low because of water movement from the intracellular to the extracellular compartment in an attempt to compensate for hyperosmolality. In patients with high plasma osmolality, and therefore greater osmotic diuresis, with inadequate fluid compensation, serum sodium can be increased. However, this is usually observed in HHS and less often in DKA. Serum sodium levels should be corrected for hyperglycemia; for each 100 mg/dl glucose >100 mg/dl (5.6 mmol/L), add 1.6 mEq to measured sodium value to obtain a corrected serum sodium value.⁶,⁸,¹⁰

Phosphorus levels in plasma are usually normal or increased. However, as in the case with potassium, the total body phosphorus deficit is large as a result of shift from the intracellular to the extracellular compartment and loss in urine.¹⁰

Most patients with DKA have leukocytosis with a left shift. This is due to dehydration and stress response to ketonemia and hyper-

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**Table 1.2** Typical water and electrolyte deficits in diabetic ketoacidosis and hyperosmolar hyperglycemic state

<table>
<thead>
<tr>
<th>Water</th>
<th>6 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>500 mmol</td>
</tr>
<tr>
<td>Chloride</td>
<td>350 mmol</td>
</tr>
<tr>
<td>Potassium</td>
<td>300–1000 mmol</td>
</tr>
<tr>
<td>Phosphate</td>
<td>50–100 mmol</td>
</tr>
<tr>
<td>Calcium</td>
<td>50–100 mmol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>25–50 mmol</td>
</tr>
</tbody>
</table>

Adapted (with modification) from reference 6 with permission.
glycemia and does not necessarily suggest infection. However, a
white cell count >25,000/μl warrants a comprehensive search for
infection. Increased hematocrit levels are found in most cases of
DKA as a result of dehydration.\(^8\)

Effective serum osmolality can be measured directly in the labo-
ratory or derived from the following formula:

\[
2 \times [\text{measured Na}^+ (\text{mEq/L})] + \text{glucose (mg/dl)}/18 = \text{mOsm/kg}
\]

or

\[
2 \times [\text{measured Na}^+ (\text{mEq/L or mmol/L})] + \text{glucose (mmol/L)} = \text{mOsm/kg}
\]

The normal range is 285–295 mOsm/kg. The level of consciousness
correlates more closely with serum osmolality than with pH. Values
>340 mOsm/kg suggest great fluid loss and are associated with
altered consciousness level (stupor or coma). However, such high
levels are not usual in DKA and are more often seen in HHS. On
the other hand, serum osmolality levels <320 mOsm/kg warrant
further evaluation for coma from causes other than DKA.\(^9,14\)

Serum amylase and lipase levels may be increased in 16% and
25% of cases, respectively, in DKA in the absence of acute pancrea-
titis.\(^17,18\) The cause of this elevation is not known. Although serum
lipase measurement is more specific for the diagnosis of pancreati-
tis, this is not true in DKA, and elevations of either amylase or lipase
to more than three times normal do not confirm the diagnosis of
pancreatitis in this situation. However, it should be noted that
coexisting acute pancreatitis may be present in 10–15% of patients
with DKA. Serum creatinine may be falsely elevated because of
acetoacetate interference with the colorimetric creatinine assay.\(^10\)

Determination of HbA\(_{1c}\) is indicative of the degree of diabetes
control in the previous 2–3 months.

**Summary box**

- DKA is a high anion gap metabolic acidosis
- Ketone bodies can be detected in serum and urine
- Although serum electrolyte levels may be normal, the total body
deficit is large
- Serum osmolality is increased
- White blood cell count and hematocrit are increased
- Serum amylase and lipase levels may be increased in the absence
  of acute pancreatitis
Differential diagnosis

Other causes of ketoacidosis need to be considered when patients with diabetes present with ketosis. These include starvation ketosis and alcoholic ketoacidosis.

Starvation ketosis evolves when a person consumes a small amount of food (<500 Kcal) for many days. However, starvation ketosis usually does not cause acidosis, blood glucose levels and osmolality are normal, and serum or urine ketones are only slightly elevated.\(^6,9\)

Pregnant women are more prone to develop ketoacidosis (pregnancy ketosis) due to starvation. This happens because pregnancy is associated with accelerated lipolysis and ketogenesis and starts within 6 hours of fasting.\(^6\) For this reason, in women of reproductive age, clinicians should consider screening for pregnancy, which has been associated with the onset of DKA.\(^19\)

Alcoholic patients may develop ketoacidosis (alcoholic ketoacidosis) after heavy drinking. Alcoholic ketoacidosis is characterized by normal or even relatively low serum glucose levels and osmolality, low pH, increased anion gap metabolic acidosis, and increased \(\beta\)-OHB concentration levels. For this reason, the results of nitroprusside-based tests for the assessment of ketosis may be normal or slightly positive.\(^6,8\)

In case of doubt, other causes of high anion gap metabolic acidosis should be considered in the differential diagnosis (lactic acidosis: measurement of plasma lactate; salicylate intoxication: salicylic acid level measurement; methanol or ethylene glycol ingestion: determination of methanol or ethylene glycol; uremic acidosis: determination of urea and creatinine).

Summary box

- Differential diagnosis of DKA includes starvation ketosis and alcoholic ketoacidosis
- In starvation ketosis, blood glucose and pH are normal, while ketones are slightly increased
- Alcoholic ketoacidosis is characterized by normal blood glucose levels and osmolality, low pH and high anion gap metabolic acidosis, as well as high \(\beta\)-OHB levels
- In case of doubt, other causes of high anion gap metabolic acidosis should be considered
Clinical management

Treatment consists of rehydration with intravenous fluids, the administration of insulin, and replacement of electrolytes. General medical care and close supervision by trained medical and nursing staff is of paramount importance in the management of patients with DKA. A treatment flowchart (Table 1.3) should be used and updated meticulously. A urine catheter is necessary if the patient is in coma or if no urine is passed in the first 4 hours.

Replacement of water deficit

Patients with DKA have severe dehydration. The amount of fluid needing to be administered depends on the degree of dehydration (Table 1.4). Fluid replacement aims at correction of the volume deficit and not to restore serum osmolality to normal. Isotonic solution NaCl (0.9%) (normal saline; osmolality 308 mOsm/kg) should be administered even in patients with high serum osmolality since this solution is hypotonic compared to the extracellular fluid of the patient.  

The initial rate of fluid administration depends on the degree of volume depletion and underlying cardiac and renal function. In a young adult with normal cardiac and/or renal function 1L of normal saline is administered intravenously within the first half- to one hour. In the second hour administer another 1 L, and between the third and the fifth hours administer 0.5–1 L per hour. Thus, the total volume in the first 5 hours should be 3.5–5 L [1]. If the patient is in shock or blood pressure does not respond to normal saline infusion, colloid solutions together with normal saline may be used.  

Some authors suggest replacement of normal saline with hypotonic (0.45%) saline solution after stabilization of the hemodynamic status of the patient and when corrected serum sodium levels are normal. However, this approach may result in rapid movement of extracellular water into cells as blood glucose and osmolality fall with treatment; such shifts have been implicated in the pathogenesis of cerebral edema. Hypotonic saline solution can be used when serum osmolality is very high; this is rare in DKA but common in HHS.

When the blood glucose level falls below 250 mg/dl (13.9 mmol/L), or according to other authors 200 mg/dl (11.1 mmol/L), normal saline should be discontinued and replaced immediately by dextrose 5% solution at a rate of 250 ml per hour. Alternatively infusion of
Table 1.3  Suggested flowchart for the monitoring of treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic state

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Mental status</th>
<th>Blood pressure</th>
<th>Pulse</th>
<th>Glucose</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>HCO₃</th>
<th>Ca</th>
<th>PO₄</th>
<th>pH</th>
<th>PaO₂/PCO₂</th>
<th>Ketones in blood</th>
<th>IV fluids</th>
<th>Insulin dose IU/h</th>
<th>Urine output</th>
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Adapted (with modification) from reference 6 with permission.
Diabetic ketoacidosis in adults

A mixture of 5% dextrose with 0.45% NaCl, instead of dextrose 5%, can be used. Glucose infusion together with insulin administration suppresses lipolysis and ketogenesis and maintains blood glucose levels at near normal (120–180 mg/dl [6.6–10 mmol/L]) levels. Intravenous glucose is given without interruption until the patient is eating again and subcutaneous insulin resumed. In total, 6–12 L of fluid may be required in the first 24 hours for the correction of dehydration. The duration of intravenous fluid administration is on average 48 hours. Restoration of water deficit requires special attention not only to the ongoing loss of fluid in the urine because hyperglycemia continues for several hours after starting treatment but also to avoid overhydration, particularly in patients with impaired cardiac or renal function. Urine output monitoring is very important for such patients.

**Intravenous soluble insulin infusion**
Administration of insulin is the etiologic treatment of DKA because it reduces blood glucose levels by inhibiting hepatic glucose production, increasing glucose uptake and utilization in peripheral tissues and inhibiting lipolysis and ketogenesis. Insulin administration must begin in parallel with fluid replacement therapy.
As recently as the early 1970s, large doses of insulin were administered for the treatment of DKA. Then several randomized trials showed that the administration of small doses of insulin is effective in the resolution of DKA and reduces the risk of hypoglycemia and hypokalemia.\textsuperscript{20,21} Nowadays, according to most protocols,\textsuperscript{1,6,8} the administration of an initial intravenous bolus of soluble rapid-acting insulin is recommended. Some suggest a bolus administration of insulin (usually 0.1 IU/kg) followed by infusion of 0.1 IU/kg per hour (usually 5–7 IU per hour). Others suggest infusion of insulin at a higher dose (0.14 IU/kg per hour) without an initial bolus administration. The infusion solution is usually prepared by adding 100 IU of insulin to 250 ml normal saline and is administered with special infusion pumps. If such pumps are not available, 50 IU of rapid-acting soluble insulin can be diluted in 500 ml normal saline, thus creating a solution with a concentration of 1 IU of insulin for every 10 ml solution, and then infusing at the desired rate (for example 50–70 ml/h if 5–7 IU per hour are needed) in parallel with the normal saline administered for the correction of dehydration using a Y connector or preferably via a separate venous line. The addition of albumin to the solution to discourage insulin absorption to the walls of the infusion device is not necessary.\textsuperscript{22}

**Other routes of insulin administration**

Instead of continuous infusion, insulin can be administered subcutaneously or intramuscularly with equally good results, providing that the patient is hemodynamically stable. Intermittent intramuscular soluble insulin administration in the deltoid muscle (5 IU) every 2 hours after an initial loading dose of 20 IU is acceptable for the treatment of uncomplicated DKA.

If subcutaneous insulin is to be used, patients typically receive an initial dose of 0.2 IU/kg (for example 16 IU in an 80 kg person) followed by 0.1 IU/kg every hour (for example 8 IU for an 80 kg person) or an initial dose of 0.3 IU/kg and subsequently 0.2 IU/kg every 2 hours while blood glucose remains above 250 mg/dl (13.9 mmol/L). When glucose levels fall to below 250 mg/dl (13.9 mmol/L) the insulin dose may be decreased by half and administered every 1 or 2 hours until resolution of DKA. Subcutaneous or intramuscular insulin is indicated for the management of DKA in centers where it is difficult to monitor low-dose intravenous infusions and may be associated with a lower cost of hospitalization by avoiding intensive care unit placement.\textsuperscript{19} Milder
forms of DKA can also be treated safely with subcutaneous or intramuscular insulin. Comparison of subcutaneous, intramuscular, and intravenous regimens for treatment of DKA has shown no significant difference in outcomes, except for a more rapid decline in glucose and ketones in the first 2 hours with the intravenous infusion.  

Recently, treatment with subcutaneous rapid-acting insulin analogs (lispro or aspart every 1 or 2 hours in non-intensive care unit settings) was shown to be an effective alternative to the use of intravenous regular insulin in the treatment of DKA. The rate of decline of blood glucose concentration and the mean duration of treatment until correction of ketoacidosis were similar among patients treated with subcutaneous insulin analogs every 1 or 2 hours or with the intravenous regular insulin. An initial intramuscular or subcutaneous dose of 0.3 IU/kg (for example, 24 IU in an 80 kg person), followed by 0.1 IU/kg every hour (for example, 8 IU every hour in an 80 kg person), can be used. However, it is recommended that until more data on efficacy are available, patients with severe DKA, hypotension, edema, or associated severe critical illness are managed with intravenous soluble insulin.

Some doctors prefer the repetitive-bolus intravenous administration of insulin: specifically the administration of 20–50 IU every 2 hours is recommended. When glucose levels fall below 250 mg/dl (13.9 mmol/L), the treatment changes to subcutaneous administration every 4–6 hours. However, because intravenous insulin has a plasma half-life of about 8–9 minutes, intermittent intravenous administration may lead to unpredictable and fluctuating insulin concentrations. In addition, high insulin doses may lead to hypokalemia and late hypoglycemia.

It should be noted that the protocols of fluid administration may vary depending on the clinic, but their basic principles and therapeutic goals remain the same. Insulin administration should produce a steady and predictable fall in blood glucose levels averaging 50–70 mg/dl per hour (2.8–3.9 mmol/L per hour). If blood glucose does not fall by at least 10% in the first hour (or less than 50 mg/dl [2.8 mmol/L per hour]) on the insulin infusion rate, the insulin dose should be doubled or increased by 0.05–0.1 IU/kg every 1–2 hours (or 1–2 IU every 1–2 hours), providing that other causes for lack of response have been excluded. These include worsening of acidosis or inadequate hydration. When blood glucose is below 250 mg/dl (13.9 mmol/L) and/or there is improvement in
clinical status with decrease in blood glucose greater than 75 mg/dl (4.2 mmol/L), the rate of insulin infusion should be decreased by 0.05–0.1 IU/kg per hour (or 1–2 IU per hour). In any case, the rate of insulin infusion should not be less than 1 IU per hour. If blood glucose has fallen to below 80 mg/dl (4.5 mmol/L), insulin infusion should be discontinued for no more than 1 hour and restarted at a lower infusion rate. During insulin infusion after the first few hours the blood glucose levels should be maintained between 140 and 180 mg/dl (7.8–10 mmol/L).\textsuperscript{1,6,10}

The intravenous infusion of insulin can be stopped when DKA has been corrected (blood glucose is less than 200 mg/dl [11 mmol/L], HCO$_3^-$ is above 18 mEq/L, pH is higher than 7.3, and anion gap is normal). Then, feeding and per os hydration as well as subcutaneous administration of insulin can be initiated.\textsuperscript{8}

Patients are given soluble insulin or rapid-acting insulin analogs 1–2 hours before discontinuation of intravenous insulin to allow sufficient time for the injected insulin to start to work and before each meal. In parallel, injection of intermediate- or long-acting insulin should be initiated to provide the basal insulin requirement. It is not recommended that patients in transition from intravenous to subcutaneous insulin only are placed on short-acting insulin using sliding scales. If patients used insulin before admission, the same dose can be restarted in the hospital. Newly diagnosed patients with Type 1 diabetes require a total daily dose of 0.5–0.8 IU/kg, divided as 30–50\% basal insulin and the remainder as rapid-acting insulin before each meal. Fingerstick glucose measurements before meals and at night should be done to correct for possible fluctuations in insulin needs.\textsuperscript{8,10}

In patients with KPD, long-term management can be guided rationally by accurate classification based upon assessment of β-cell functional reserve, β-cell autoantibodies, and in some instances, HLA allelotyping. Although assessment of these parameters in all patients presenting with DKA is ideal, cost constraints and assay availability may make it prohibitive in some regions.

At presentation the type of diabetes is unknown and it is advisable that all patients continue subcutaneous insulin administration on discharge from the hospital until further testing (β-cell functional reserve and pancreatic autoantibodies) is performed. Assessment of β-cell secretory reserve and β-cell autoimmunity can be performed 1–3 weeks after resolution of ketoacidosis, to minimize the acute effects of glucose toxicity or desensitization on
β-cell function. β-Cell secretory reserve (as measured by fasting plasma C-peptide, C-peptide response to glucagon stimulation, and C-peptide to glucose ratio) following DKA resolution is the strongest predictor of long-term glycemic control and insulin dependence. Patients are classified as “β−” if the fasting serum C-peptide concentration is less than 1 ng/ml (0.33 nmol/L) and the peak serum C-peptide response to glucagon (measured at 5 and 10 minutes after intravenous injection of 1 mg glucagon) is less than 1.5 ng/ml (0.5 nmol/L). Although these cut-off points do not independently predict the potential for successful and safe withdrawal of insulin, a high ratio (>11) of fasting C-peptide (in nmol/L) to glucose (in mmol/L) at 6 months predicts such a course among β+ patients.

Patients with poor β-cell function (β−) after resolution of the DKA event typically require long-term exogenous insulin therapy, regardless of autoantibody status. Patients with β-cell secretory reserve who are antibody negative (A−β+) are often able to discontinue insulin, especially if they had unprovoked DKA as the initial manifestation of diabetes. The duration of the process of insulin withdrawal is variable and may range from 10 to 14 weeks to longer. If, after discontinuation of insulin, blood glucose values increase without development of ketosis, treatment with oral or injectable agents to lower blood glucose is required. If the patient develops ketosis upon decreasing the insulin dose, insulin should be intensified. In this setting, attempting to withdraw insulin a second time is not suggested. Patients with preserved β-cell function who have autoantibodies (A+β+) have a variable course, with some demonstrating progressive β-cell deterioration and others long-term preservation. This group of individuals requires more careful monitoring, and these patients may benefit from HLA genotyping to provide additional prognostic markers of clinical behavior.

Ketonemia and ketonuria may continue for up to 36 hours because of the slow elimination of ketone bodies. When ketonemia is used to assess response to therapy, determination of β-OHB in blood is recommended.

**Treatment of acidosis**

Most experts do not recommend the administration of bicarbonate because acidosis is corrected with insulin infusion and rehydration. The administration of bicarbonate in severe acidosis (pH less than
7.0) remains controversial. Severe metabolic acidosis exerts a negative inotropic effect on the heart, induces vasodilation and hypotension, reduces glucose uptake and utilization, and promotes ventricular arrhythmias. On the other hand, bicarbonate therapy may lead to worsening of hypokalemia (especially at the beginning of bicarbonate administration), intracellular acidosis in the central nervous system (paradoxical acidosis), and metabolic alkalosis. One study showed that bicarbonate administration had no benefits for patients with DKA and initial pH 6.9–7.15. However, in this trial the number of patients with pH in this range was very small. Based on existing evidence and expert opinion, it may be prudent to administer 50 mmol of bicarbonate in 200 ml water with 10 mEq of potassium chloride over 1 hour in patients whose pH is 6.9–7.0 or serum bicarbonate less than 5 mEq/L. In patients with pH less than 6.9, doubling of the above bicarbonate dose is recommended. Arterial pH should be monitored 2 hours later and the dose should be repeated if pH remains lower than 7.0.

**Electrolyte replacement**

Replacement of sodium and chloride deficits is achieved by the administration of normal saline as described above. Particular attention should be paid to potassium restoration. As mentioned, serum potassium concentrations are usually normal or increased despite the significant total body deficit. During treatment of DKA potassium levels are decreased, sometimes very quickly, because correction of acidosis and the insulin infusion move potassium into the intracellular compartment. Hypokalemia may cause severe arrhythmias and cardiac arrest. If potassium levels are less than 3.3 mEq/L at any point during therapy, insulin should be stopped and potassium should be administered. Potassium replacement must be performed as follows.

- Low potassium (less than 3.3 mEq/L): insulin should be immediately discontinued; give 20–30 mEq of potassium per hour until potassium levels exceed 3.3 mEq/L; then resume insulin infusion.
- Potassium levels between 3.3 and 5.3 mEq/L: add 20–30 mEq of potassium in each liter of intravenously administered fluid to keep serum potassium between 4 and 5 mEq/L.
- Potassium levels above 5.3 mEq/L: potassium is not administered until levels reach the normal value. Repeat potassium measurement in 2 hours.
Potassium is replaced as KCl. Some authors recommend replacement of one third of the potassium with KPO₄ to avoid excessive chloride administration and to prevent hypophosphatemia. Special attention is needed in patients with impaired renal function or anuria to avoid hyperkalemia.

It should be noted that the goal of treatment is not immediate restoration of the total potassium deficit. This can be done progressively and completed with feeding.

Phosphate depletion is common in DKA, and serum phosphate levels may decline during treatment with insulin because phosphate is taken up intracellularly. However, phosphate replacement should be reserved only for patients with severe hypophosphatemia (serum levels <1.5 mg/dl [0.48 mmol/L]) providing that serum calcium levels are normal. Oral phosphate repletion is always preferable to intravenous repletion and should be commenced as soon as patients are able to take food by mouth. The management of DKA is depicted in Figure 1.2.

Summary box

- Treatment of DKA includes rehydration, insulin administration, and correction of electrolyte deficit
- Administer 3.5–5 L of normal saline in the first 5 hours and 6–12 L in the first 24 hours
- The average duration of fluid administration is 48 hours
- Intravenous infusion of insulin is preferable to intramuscular or subcutaneous injection
- Pay particular attention to the correction of hypokalemia
- Once the patient can eat, discontinue intravenous insulin and start subcutaneous intermediate- or long-acting insulin together with preprandial rapid-acting insulin
- Correction of metabolic acidosis may be indicated when arterial pH is less than 7.0

Patient monitoring

The protocol in Table 1.5 is suggested for the monitoring of patients with DKA and should be meticulously completed (see Table 1.3) (it may vary between clinics).
Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain arterial blood for measurement of gases and venous blood for metabolic profile. Start IV fluids: 1 L of 0.9% NaCl per hour

**Figure 1.2** Proposed algorithm for the treatment of diabetic ketoacidosis (Modified from Reference 9).

**IV fluids**
- Determine hydration status
  - Severe hypovolemia
    - Administer 0.9% NaCl (1 L/h)
  - Mild dehydration
    - Hemodynamic monitoring
      - Administer 0.9% NaCl (1 L/h) + colloids
    - Administer 0.9% NaCl 250–500 ml/h depending on hydration status
  - Shock
    - Administer 0.9% NaCl 500–1000 ml/h depending on hydration status

**Bicarbonate**
- pH 6.9–7.0
  - 50 mmol HCO$_3^-$ plus 10 mEq KCl in 200 ml water; administer in 1 h
  - Hemodynamic monitoring
    - Administer 0.9% NaCl (1 L/h) + colloids
- pH < 6.9
  - 100 mmol HCO$_3^-$ plus 20 mEq KCl in 200 ml water; administer in 2 h
  - Repeat every 2 h until pH ≥ 7.0. Monitor serum K$^+$ every 2 h

**Soluble insulin**
- pH ≥ 7.0
  - 0.1 IU/kg bolus IV
  - 0.1 IU/kg/h as continuous insulin infusion
  - If serum glucose does not fall by at least 10% in first hour, the insulin dose should be doubled or increased by 0.05–0.1 IU/kg (usually 1–2 IU) every 1–2 hours
  - When serum glucose reaches 250 mg/dl, reduce insulin infusion serum to 0.2–0.05 IU/kg/h.
  - Keep serum glucose between 150 and 200 mg/dl until resolution of DKA

**Potassium**
- pH < 6.9
  - No HCO$_3^-$
  - 0.1 IU/kg/h as continuous insulin infusion
  - Hold insulin and give 20–30 mEq KCl until K$^+$ > 3.3 mEq/L
- pH ≥ 7.0
  - 0.1 IU/kg/h as continuous insulin infusion
  - If serum glucose does not fall by at least 10% in first hour, the insulin dose should be doubled or increased by 0.05–0.1 IU/kg (usually 1–2 IU) every 1–2 hours
  - When serum glucose reaches 250 mg/dl, reduce insulin infusion serum to 0.2–0.05 IU/kg/h.
  - Keep serum glucose between 150 and 200 mg/dl until resolution of DKA

**Potassium**
- K$^+$ ≤ 3.3 mEq/L
  - Give 20–30 mEq in each liter of IV fluid to keep serum K$^+$ between 4 and 5 mEq/L
- K$^+$ > 5.2 mEq/L
  - Do not give K$^+$ but check serum K$^+$ every 2 h

Check electrolytes, urea or BUN, creatinine and glucose every 2–4 hrs until stable. After resolution of DKA and when patient is able to eat, initiate SC multidose insulin regimen. To transfer from IV to SC, continue IV insulin infusion for 1–2 hours after SC insulin begun to ensure adequate serum insulin levels. In insulin naïve patients, start at 0.5–0.8 IU/kg per day and adjust as needed. Always examine for precipitating causes to prevent recurrence.
Complications of DKA include hypoglycemia (due to overtreatment), hypokalemia, cerebral edema, non-anion gap hyperchloremic acidosis, fluid overload, rhinocerebral mucormycosis, thrombotic events, rhabdomyolysis, and acute respiratory distress syndrome.\textsuperscript{1,6,8,10}

Administration of large doses of insulin for the management of DKA was associated with hypoglycemia, which sometimes was severe. Hypoglycemia is less commonly seen with the use of low-dose insulin regimens and with regular blood glucose monitoring as well as a fluid change to glucose 5% solution when blood glucose falls below 250 mg/dl (13.9 mmol/L).\textsuperscript{8}

Hypokalemia can be prevented with appropriate potassium replacement and frequent monitoring. As mentioned above, insulin infusion should be discontinued when serum potassium falls to levels lower than 3.3 mEq/L at any stage of treatment and immediate potassium administration should begin.\textsuperscript{8,10}

Cerebral edema is a very rare complication in adults. It has been described in young adults presenting with DKA and is seen in 1–2% of children presenting with DKA. However, subclinical cerebral edema, demonstrable by computed tomography (CT) scanning or raised cerebrovascular fluid pressure, probably occurs in most cases during or even before treatment.\textsuperscript{10,29} It is manifested by headache,
decline in consciousness level often progressing rapidly to coma, pupillary changes, vomiting, elevated diastolic blood pressure, decorticate or decerebrate posturing, cranial nerve palsies, Cheyne–Stokes respiration, and seizures. Typically it occurs within 8–24 hours after initiation of treatment and many patients deteriorate without warning. The mortality rate is high (70–90%) and may be partially related to delayed diagnosis and treatment. Mechanisms underlying this condition include rapid decline in plasma osmolality (greater than 3% per hour), high intravascular fluid replacement rate, use of hypotonic fluids, and high rate of decrease in blood glucose. The diagnosis can be confirmed by CT or magnetic resonance scanning, which shows swelling of the brain with loss of structural details and squashing of the ventricular system. Treatment of cerebral edema includes administration of mannitol (0.3 g/kg given over 30 minutes and repeated hourly if there is no improvement to single doses of 1 g/kg). Dexamethasone is often given in high doses (4 mg every 6 hours intravenously) but its benefit remains unproven. Mechanical ventilation to remove carbon dioxide and improve acidosis has also been advocated.

Non-anion gap hyperchloremic acidosis may occur because chloride is preferentially reabsorbed in the proximal renal tubules and chloride losses are less than sodium losses in DKA. Because replacement solutions have equal amounts of sodium and chloride, relative hyperchloremia may occur with treatment. The development of acidosis should not affect the treatment course and usually resolves.

Fluid overload may be seen in patients with severe cardiac or renal impairment. In addition, acute respiratory distress syndrome has been reported in patients less than 50 years of age who are free of cardiac or renal disease. Manifestations include dyspnea, tachypnea, and central cyanosis. Arterial hypoxia is characteristic and chest radiograph reveals bilateral pulmonary infiltrates. The development of new pulmonary rales and an increased alveolar–arterial oxygen gradient are clues to diagnosis. Patients with this syndrome need mechanical support of ventilation and avoidance of fluid overload.

Rhinocerebral mucormycosis may develop in patients who develop recurrent episodes of DKA or another metabolic acidosis. This is caused by an opportunistic fungal infection starting in the paranasal sinuses and rapidly invading adjacent tissues (nose, sinuses, orbit, and brain). Treatment comprises of correction of acidosis, surgical excision of the affected tissues, and intravenous administration of antifungal agents.
Diabetic ketoacidosis in adults

Diabetes is characterized by a propensity to thrombosis. Marked hyperglycemia is associated with decreased blood flow, increased blood viscosity, and increased coagulability. The role of prophylactic anticoagulation has not been clearly established. Because many patients present with some degree of renal failure, unfractionated heparin use is preferred for prevention of thromboembolism.\(^{10}\)

Rhabdomyolysis is another possible complication of DKA. Hyperosmolalality and hypoperfusion contribute to skeletal muscle damage. Recent data suggest that DKA is more common among users of cocaine, a common cause of rhabdomyolysis. Creatinine phosphokinase levels can be initially assessed in patients with DKA if clinically indicated.\(^{10}\)

**Summary box**

- The most common but preventable complications of DKA are hypoglycemia and hypokalemia
- Rare complications are cerebral edema, non-anion gap hyperchloremic acidosis, fluid overload, rhinocerebral mucormycosis, thrombotic events, rhabdomyolysis, and acute respiratory distress syndrome

**Prevention**

Many cases of DKA can be prevented by better access to medical care, proper education and effective communication with a healthcare provider during an intercurrent illness. Sick-day rules should be reviewed periodically with all patients (see Chapter 8). The patients and/or their family members must be able to determine blood glucose and β-OHB or urine ketones when blood glucose levels are above 300 mg/dl (16.7 mmol/L). Many hospitalizations can be avoided by devoting adequate resources to apply the measures described above.\(^{8}\)

**Summary box**

- The majority of DKA cases can be prevented by better access to medical care and proper education
- Sick-day rules must be reviewed periodically with all patients
- All patients with diabetes should be educated to monitor blood or urine for ketones when blood glucose levels are higher than 300 mg/dl (16.7 mmol/L)
Case studies

Case study 1.1
A 32-year-old male with Type 1 diabetes since the age of 14 years was taken to the emergency room because of drowsiness, fever, cough, diffuse abdominal pain, and vomiting. Fever and cough started 2 days ago and the patient could not eat or drink water. He has been treated with an intensive insulin regimen (insulin glargine 24IU at bedtime and a rapid-acting insulin analog before each meal). On examination he was tachypneic, his temperature was 39°C (102.2°F), pulse rate 104 beats per minute, respiratory rate 24 breaths per minute, supine blood pressure 100/70 mmHg; he also had dry mucous membranes, poor skin turgor, and rales in the right lower chest. He was slightly confused. Rapid hematology and biochemical tests showed hematocrit 48%, hemoglobin 14.3 g/dl (143 g/L), white blood cell count 18,000/μl, glucose 450 mg/dl (25.0 mmol/L), urea 60 mg/dl (10.2 mmol/L), creatinine 1.4 mg/dl (123.7 μmol/L), Na⁺ 152 mEq/L, K⁺ 5.3 mEq/L, PO₄³⁻ 2.3 mEq/L (0.74 mmol/L), and Cl⁻ 110 mmol/L. Arterial pH was 6.9, PO₂ 95 mmHg, PCO₂ 28 mmHg, HCO₃⁻ 9 mEq/L, and O₂ sat 98%. The result of the strip for ketone bodies in urine was strongly positive and the concentration of β-OHB in serum was 3.5 mmol/L. Urinalysis showed glucose 800 mg/dl and specific gravity 1030.

What is your diagnosis?
The patient has hyperglycemia, ketosis, and metabolic acidosis. Therefore, he has DKA. In addition, because of the pre-existing fever, cough, localized rales on auscultation and high white blood cell count, a respiratory tract infection should be considered. The patient is also dehydrated and has impaired renal function.

Do you need more tests to confirm the diagnosis?
Determination of the effective serum osmolality and anion gap should be performed in all patients presenting with potential DKA. Serum osmolality can be measured directly in the laboratory or be calculated. Calculated effective serum osmolality in this case was 329 mOsm/kg and the anion gap is 33 mEq/L. Typically DKA is a high anion gap metabolic acidosis while serum osmolality may vary from normal to high. In addition a chest X-ray should be performed and blood cultures be obtained to check for lower respiratory tract infection and isolate the pathogenic bacteria.
How will you manage this patient?
Immediate infusion of normal saline and intravenous insulin should be initiated as described in the text. Because his serum potassium level is in the normal range, 10 mEq of potassium should be added to each liter of normal saline infused. Serum potassium levels should be checked at 2, 6, 10, and 24 hours and appropriate adjustment to the dose must be made. In addition, 100 ml of bicarbonate plus 10 mEq of potassium in 200 ml of water can be administered in 1 hour because pH is 6.9 and plasma bicarbonate levels are low. Arterial pH and bicarbonate should be re-checked in 30 minutes and, if uncorrected, infusion of a similar or lower amount of bicarbonate should be repeated as discussed in the text. If infection is confirmed, intravenous administration of antibiotics should begin while waiting for the results of blood cultures.

The patient was treated with fluids and electrolyte replacement and intravenous insulin for 48 hours. Afterwards, his blood glucose was 150 mg/dl (8.3 mmol/L), fever, nausea, vomiting and abdominal pain resolved, and he was able to eat and to drink water.

What is your next step?
The patient can start to eat and drink water. Intravenous insulin can safely be discontinued and subcutaneous insulin begun. A bolus of rapid-acting insulin should be administered subcutaneously based on the results of the fingerstick test 1–2 hours before discontinuation of intravenous insulin, and 24 IU of basal insulin should be started.

A careful history should be obtained to determine the cause of DKA and to avoid recurrence. This patient was not aware of the sick-day rules and had never been instructed to check often or how to correct high blood glucose values. Because he was not able to eat and drink water he reduced both the basal and the preprandial insulin to avoid hypoglycemia. The patient was educated about sick-day rules and to check urine and blood for ketones if blood glucose is above 300 mg/dl (16.7 mmol/L).

Case study 1.2
An 18-year-old female was taken to the emergency room in coma. Her parents noticed that she had polydipsia, polyuria, and rapid weight loss which started approximately 1 month ago and had worsened in the last week. She had not been taking any
medications and the clinical history was otherwise unremarkable. On examination, breathing was deep and rapid (Kussmaul respiration), pulse rate was 100 beats per minute, and blood pressure 110/70 mmHg; she also had signs of dehydration. She was drowsy and confused. Rapid hematology and biochemical tests showed hematocrit 44%, hemoglobin 13 g/dl (140 g/L), white blood cell count 12,000/μl, glucose 520 mg/dl (28.9 mmol/L), urea 50 mg/dl (8.5 mmol/L), creatinine 0.8 mg/dl (70.7 μmol/L), Na⁺ 148 mEq/L, K⁺ 4.6 mEq/L, PO₄⁻ 2.0 mEq/L (0.64 mmol/L), and Cl⁻ 112 mmol/L. Arterial pH was 7.0, PO₂ 98 mmHg, PCO₂ 25 mmHg, HCO₃⁻ 12 mEq/L, and O₂sat 98%.

What is your diagnosis?
The patient has marked hyperglycemia and metabolic acidosis. The diagnosis of newly diagnosed Type 1 diabetes presenting with DKA should be considered.

Which additional biochemical tests are required to confirm the diagnosis?
Determination of ketone bodies in blood or urine is necessary to confirm ketosis. In this case the strip for ketones in the urine was strongly positive and determination of β-OHB in serum was 4.0 mmol/L. Thus, the patient has the triad of hyperglycemia, ketosis, and acidosis and the diagnosis of DKA is confirmed.

How will you manage the patient?
Urgent administration of intravenous fluid and insulin should begin together with careful monitoring, replacement of electrolytes, and correction of acidosis. After resolution of DKA and as long as the patient is conscious, feeding can start. Transition from intravenous to subcutaneous insulin administration should begin. A bolus of rapid-acting insulin should be administered subcutaneously based on the results of the fingerstick test 1–2 hours before discontinuation of intravenous insulin. A total daily dose of insulin of 0.5–0.8 IU/kg is required, divided as 30–50% basal insulin and the remainder as rapid-acting insulin before each meal.

References
Diabetic ketoacidosis in adults


